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REMARKS

A check for $55 for the fee for a one-month extension of time accompanies this response. Any fee that may be due in connection with this application may be charged to Deposit Account No. Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 70, 72-79, 92-94, 123, 124, 127-133 and 135-138 are pending in this application.

Claims 70, 74 and 124 are amended herein to replace the recitation "variable" with the recitation –random–, basis for which is found throughout the specification (se, *e.g.*, page 20, line 25 through page 21, line 8 and the original claims as filed). Claim 124 is further amended to replace the recitation "4^n" with -4^R-. Basis for the amendment is found throughout the specification (for example, see page 11, lines 21-23 and the original claims as filed). Claims 75 and 137 are amended herein to more distinctly recite that the array is fixed to a solid support. Basis for the amendment is found throughout the application (for example, see page 6, lines 6-7 and page 8, lines 5-7). Claim 136 is amended to replace the recitation "constant portion" with the recitation –double-stranded portion–, basis for which is found throughout the specification (for example, see page 20, lines 1-2).

Therefore, no new matter is added. The amendments should place the claims and the application into condition for allowance.

REJECTION OF CLAIMS 70, 72, 73 AND 77-79 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 70, 72, 73 and 77-79 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application. The Examiner alleges that the specification does not

provide adequate support for the recitation "wherein the variable sequence is not at the terminus" in claim 70.

Applicant respectfully traverses the rejection.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific [claimed embodiment] *Vas-Cath, Inc. v. Mahurkar*, at 1115, quoting *In re Ruschig*, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is

whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the **subject matter of the claim need not be described literally (i.e., using the same terms or inhaec verba)** in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

The guidelines promulgated by the U.S. PTO embody these rules:

In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:

(1) identify the claim limitation not described; and

(2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

The Instant Claims

Claim 70 is directed to an array of nucleic acid probes, where each probe has a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence within the single-stranded portion, where the random sequence is not at the terminus. Claims 72, 73 and 77-79 ultimately depend from claim 70 and are directed to various embodiments thereof.

ANALYSIS

In this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed. It is respectfully submitted that, at the time of application, applicant appreciated and was in possession of an array of probes as instantly claimed in claim 70 where the random sequence is within the single-stranded region and is not at the terminus.

Merriam Webster's Collegiate Dictionary defines "within" as:

[1]within (adverb) 1. in or into the interior : inside ...
[2]within (preposition) 1. used as a function word to indicate enclosure or containment; ... 3. to the inside of : into
[3]within (noun) an inner place or area
[4]within (adjective) being inside : enclosed

(Tenth ed., 1995, page 1359). Thus, when given its ordinary meaning, the word "within" as used in the recitation "variable nucleotide sequence within the single-stranded region" connotes being in the interior of or inside of the single-stranded region. In the disclosure of the application, applicant distinguishes between a random sequence "within" a single-stranded portion and a random

sequence at a terminus of a single-stranded portion. For example, the specification teaches arrays of probes where the random sequence is at a terminus (page 6, lines 10-15):

> Another embodiment of the invention is directed to methods for creating arrays of probes comprising the steps of synthesizing a first set of nucleic acids each comprising a constant sequence of length C at the 3'-terminus, and a random sequence of length R at the 5'- terminus, synthesizing a second set of nucleic acids each comprising a sequence complimentary to the constant sequence of the first nucleic acid, and hybridizing the first set with the second set to form the array.

The specification also teaches arrays of probes that include a variable sequence **within** the single-stranded region (for example, page 6, lines 3-9):

> One embodiment of the invention is directed to arrays of 4^R different nucleic acid probes wherein each probe comprises a double-stranded portion of length D, a terminal single-stranded portion of length S, and a random nucleotide sequence within the single-stranded portion of length R. These arrays may be bound to solid supports and are useful for determining the nucleotide sequence of unknown nucleic acids and for the detection, identification and purification of target nucleic acids in biological samples.

Thus, at the time of application, applicant discloses, in one embodiment, an array of probes where the random sequence is at a terminus and, in another embodiment, an array of probes where each probe includes a random sequence within (in the interior of or inside of) the single-stranded region. Having described the characteristics of the various embodiments of the arrays of probes, the specification goes on to set forth methods of making the arrays. The instant specification teaches a number of methods to create an array of probes that include a random sequence that is in the interior of or inside of the single-stranded region. For example, page 27, lines 6-25 discloses:

> Another embodiment of the invention is directed to a method for creating a nucleic acid probe comprising the steps of (a) synthesizing a plurality of single-stranded first nucleic acids and a set of longer single-stranded second nucleic acids complimentary to the first nucleic acid with a random terminal nucleotide sequence, (b) hybridizing the first nucleic acids to the second nucleic acids to form hybrids having a double-stranded portion and a single-

> stranded portion with the random nucleotide sequence in the single-stranded portion, (c) hybridizing a single-stranded nucleic acid target to the hybrids, (d) ligating the hybridized target to the first nucleic acid of the hybrid, (e) enzymatically extending the second nucleic acid using the target as a template, (f) isolating the extended second nucleic acid, and (g) hybridizing the first nucleic acid of step (a) with the isolated second nucleic acid to form a nucleic acid probe.

Thus, the specification discloses an embodiment where the probes include a double-stranded region and a single-stranded region, where the single-stranded region includes a random nucleotide sequence within the single-stranded portion, and where the single-stranded portion is terminated by an enzymatic extension product. Because the enzymatic extension uses the target as the template, the enzymatic extension product is not random. Hence, the random sequence is not at the terminus. Therefore, applicant discloses in the specification an array of probes where each probe has a double-stranded region, a terminal single-stranded region and a random nucleotide sequence that is within the single-stranded region and not at the terminus.

Thus, because there is sufficient written description as to the characteristics of the various embodiments of the arrays of probes and methods of making the arrays, it is respectfully submitted that an array of probes as instantly claimed in claim 70 finds basis in the specification as filed. Applicant respectfully submits that the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant contemplated and was in possession of an array of probes as instantly claimed in claim 70 where each probe includes a random sequence that is not at the terminus of the single-stranded region. No new matter is added.

REJECTION OF CLAIMS 74-76, 92-94, 123, 124 AND 136 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 74-76, 92-94, 123, 124 and 136 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject

matter at the time of filing of the application. The Examiner alleges that the specification does not provide adequate support for the recitation "a variable terminal nucleotide sequence of between about 3-10 nucleotides in length" in claim 74.

Applicant respectfully traverses the rejection.

RELEVANT LAW

See related section above.

The Instant Claims

Claim 74 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Claims 75, 76, 92-94, 123, 124 and 136 depend from claim 74 and are directed to various embodiments thereof.

ANALYSIS

It is respectfully submitted that the rejection is obviated by amendment of the claims herein to replace the recitation "variable" with the recitation –random– as originally claimed. The specification teaches an array of probes having a random terminal nucleotide sequence of between about 3-10 nucleotides in length. For example, the specification teaches at page 20, line 28 through page 21, line 8 that in one embodiment, the claimed subject matter

> is directed to a method for creating probe arrays comprising the steps of synthesizing a first set of nucleic acids each comprising a constant sequence of length C at a 3'- terminus and a random sequence of length R at a 5'-terminus, synthesizing a second set of

> nucleic acids each comprising a sequence complimentary to the constant sequence of each of the first nucleic acid, and hybridizing the first set with the second set to create the array. Preferably, the nucleic acids of the first set are each between about 15-30 nucleotides in length and the nucleic acids of the second set are each between about 10-25 nucleotides in length. Also preferable is that C is between about 7-20 nucleotides and R is between about 3-10 nucleotides.

Hence, the specification provides adequate description for an array of probes that include a random nucleotide sequence between about 3-10 nucleotides. It is respectfully submitted that the skilled artisan would recognize that an array of probes having a random nucleotide sequence of a length between about 3-10 nucleotides as instantly claimed in claim 74 was contemplated at the time of filing of this application. No new matter has been added.

REJECTION OF CLAIMS 127-133, 135, 137 AND 138 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 127-133, 135, 137 and 138 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application. The Examiner alleges that the specification does not provide adequate support for the recitations "each probe comprises a predetermined sequence of fixed and non-fixed positions; and the array is divided into subarrays, wherein for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base" in claim 127. The Examiner alleges that Macevicz does not provide basis for the recitations, and contends that "applicant appears to be extrapolating from Macevicz terminology and structure not clearly defined by the reference" and the amendments thus allegedly constitute new matter.

Applicant respectfully traverses the rejection.

RELEVANT LAW

See related section above.

The Instant Claims

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a random nucleotide sequence within the single-stranded portion, where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions; and the array is divided into subarrays, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base. Claims 128-133, 135, 137 and 138 depend from claim 127 and are directed to various embodiments thereof.

ANALYSIS

It is respectfully submitted that, at the time of application, applicant appreciated and was in possession of an array of probes as instantly claimed in claim 74. The specification provide basis for each of the recitations of the claimed subject matter.

Predetermined Sequence of Fixed and Non-fixed Positions

The specification teaches that the probes of the array include a predetermined sequence of fixed and non-fixed positions. For example, Macevicz (International Patent Application, US89-04741, published 1989, WO 90/04652, which is incorporated by reference in the instant application) teaches at page 5, line 2 through page 6, line 9 that

> It is not critical that the probes all have the same length, although it is important that they have known lengths and that **their sequences be predetermined**. Generally, the probes will be fixed at a predetermined number of positions with known bases (not necessarily of the same kind), e.g. as the A in Formula I, and the remaining positions will each be filled by a base randomly selected from a predetermined set, e.g. T, G, and C as in Formula I, or I and

> C as in Formula II. The positions in a probe which are nondegenerate in their base pairing, i.e. have only a single natural base, are referred to herein as fixed positions. The bases occupying fixed positions are referred to herein as fixed bases. For example, the fixed bases in the probes of Formulas I and II are deoxyadenosine at positions one, two, five, and eight with respect to the 3' end of the probe. [*emphasis added*]
>
> Generally, sets and/or subsets of the invention each contain at least one probe having a sequence of fixed and non-fixed positions equivalent to that of each permutation of a plurality of fixed and non-fixed positions less than or equal to the length of the probe. That is, an important feature of the invention is that **the probes collectively contain subsequences of fixed and non-fixed positions** (which may be the total length of the probe, as is the case for the probe sequences of Appendix I) which correspond to every possible permutation of fixed and non-fixed positions of each of a plurality of combinations of fixed and non-fixed positions, the plurality including combinations containing from zero to all fixed positions. For example, consider a subset of probes of the invention that consists of 8-mer probes whose fixed positions contain only deoxyadenosine and whose initial (i.e., 3'-most) position is fixed. The probes of Formulas I and II are members of such a subset. Within such a subset, there is at least one probe having a subsequence of fixed and non-fixed positions in positions 2 through 8 which corresponds to each possible permutation of fixed and non-fixed positions for subsequences having no fixed positions (one such permutation: A0000000), one fixed position (seven such permutations, e.g. A000A000), two fixed positions (twenty-one such permutations, e.g. A00AA000), three fixed positions (thirty-five such permutations, e.g. A0000AAA), four fixed positions (thirty-five such permutations, e.g. A0AAAA00), five fixed positions (twenty-one such permutations, e.g. AAA00AAA), six fixed positions (seven such permutations, e.g. AAAA0AAA), and seven fixed positions (one such permutation: AAAAAAAA). Thus, the subset has at least $1+7+21+35+35+21+7+1=128$ members. [*emphasis added*]

Thus, the specification provides adequate description of an array of probes where at least one of the probes of the array includes a predetermined sequence of fixed and non-fixed positions as instantly claimed. Hence, it is respectfully submitted that the skilled artisan would recognize that an array of probes as instantly claimed in claim 127 where each probe includes a

predetermined sequence of fixed and non-fixed positions was contemplated at the time of filing of this application. No new matter has been added.

The Array is Divided into Subarrays

The specification teaches that the claimed array is divided into subarrays, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base. For example, Macevicz teaches at page 3, lines 17-29 that

> In one embodiment of the invention, **the set of probes comprises four subsets**. Each of the four subsets contains probes representing every possible sequence, with respect to the size of the probe (which is predetermined), **of only one of the four bases**. For example, the first subset can contain probes where every possible sequence of G is represented; the second subset can contain probes where every possible sequence of T is represented; and so on for C and A. [*emphasis added*]

Further, the instant specification teaches at page 12, lines 3-9 that:

> The probes are divided into four subsets. **In each, one of the four bases is used at a defined number of positions and all other bases except that one on the remaining positions**. Probes from the first subset contain two elements, A and non-A (A = adenosine). For a nucleic acid sequence of length k, there are $4(2^{k-1})$, instead of 4^k probes. Where k = 8, a set of probes would consist of only 1020 different members instead of the entire set of 65,536. The savings in time and expense would be considerable.

Hence, the specification provides adequate support for the recitation "each probe comprises a predetermined sequence of fixed and non-fixed positions; and the array is divided into subarrays, wherein for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base" in claim 127. Hence, applicant is not "extrapolating from Macevicz terminology and structure not clearly defined by the reference" as alleged by the Examiner. The claimed subject matter is supported by the specification. Thus,

applicant was in possession of an array of probes having the claimed characteristics at time of application. Therefore, applicant respectfully submits that the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the claimed subject matter. No new matter has been added.

REJECTION OF CLAIMS 75, 136 AND 137 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 75, 136 and 137 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter.

This rejection is respectfully traversed.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. S*hatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

THE CLAIMS

Claim 75 is directed to the array of claim 74, where the array is fixed to a solid support selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Claim 136 is directed to the array of claim 74, where the double-stranded portion of each probe includes an enzyme recognition site.

Claim 137 is directed to the array of claim 127, where the array is fixed to a solid support.

ANALYSIS

CLAIMS 75 AND 137

The Examiner alleges that it is unclear whether the recitation "which is fixed to a solid support" in both claim 75 and claim 137 is intended to limit the nucleic acid probes or the claimed array. Applicant respectfully submits that both claims recite in plain language "the array ... which is fixed to a solid support." Applicant sees no ambiguity in the instant claim language. Further, if the claim language was construed to mean that the "nucleic acid probes" are fixed to a solid support, applicant submits that the resulting composition is equivalent, because "the array" is an "array of nucleic acid probes." In the interest of advancing the prosecution of this application to allowance, claims 75 and 137 are amended herein to recite "wherein the array is fixed to a solid support."

CLAIM 136

The Examiner alleges that there is no antecedent basis for the recitation "the constant portion" in claim 74. Applicant respectfully submits that this rejection is obviated by the amendment of claim 136 herein, which replaces the recitation "the constant portion" with the recitation –the double-stranded portion–, for which claim 74 provides adequate basis.

THE REJECTION OF CLAIMS 70, 72, 74, 76-79, 92-94, 124, 127, 129-131, 133 AND 135-137 UNDER 35 U.S.C. § 102(e)

Claims 70, 72, 74, 76-79, 92-94, 124, 127, 129-131, 133 and 135-137 are rejected under 35 U.S.C. § 102(e) as anticipated by Deugau *et al.* (U.S. Patent No. 5,508,169) because Deugau *et al.* allegedly discloses an array of nucleic acid probes having a double-stranded portion at the 3'-terminus and a single-stranded portion at the 5'-terminus (Fig. 2; column 11, lines 14-25; and

column 9, lines 28-42). The Examiner alleges that the claims have been amended to introduce numerous method steps for making the array of probes (e.g., hybridizing, ligating, predetermined, divided, selected) and that these method limitations in the apparatus claims are given little patentable weight because the determination of patentability is based on the product itself and not on its method of production.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 70 is directed to an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence within the single-stranded portion, where the random sequence is not at the terminus. Claims 72, 73 and 77-79 depend from claim 70 and are directed to various embodiments thereof.

Claim 74 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Claims 75, 76, 92-94, 123, 124 and 136 depend from claim 74 and are directed to various embodiments thereof.

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions, and the array is divided into subarrays, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base. Claims 128-133, 135, 137 and 138 depend from claim 127 and are directed to various embodiments thereof.

Disclosure of Deugau *et al.*

Deugau *et al.* discloses indexing linkers that have single-stranded portions on both ends or on only one end. The reference discloses that the double-stranded portion can be at either the 3'-terminus or at the 5'-terminus. Deugau *et al.* discloses that the indexing linkers have a protruding single strand of a unique sequence of 3, 4, or 5 nucleotides, and that neither single-stranded end will function as a restriction endonuclease recognition site. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction

endonucleases, which produce protruding overhangs on each end of a fragment (col. 7, lines 48-60). Deugau *et al.* discloses that the minimum number of identifiable probes required for a comprehensive panel containing N-nucleotide protruding ends is $[N \times (N+1)] \div 2$ (where N is equal to 4^R, where R is 3, 4, or 5) (see col. 7, lines 48-64).

Differences between the claimed subject matter and the disclosure of Deugau *et al.*

Claims 70, 72, 73 and 77-79

The Examiner alleges that Deugau *et al.* discloses an array of probes as instantly claimed because Deugau *et al.* discloses an array of probes that includes a double-stranded portion and a single-stranded portion that varies in length. The Examiner alleges that the instant specification defines "variable" as varying in length, citing page 30, line 10, and thus concludes that Deugau *et al.* discloses a "variable" sequence. Applicant respectfully disagrees. The specification teaches at page 30, lines 2-11 that:

> The basic sequencing by hybridization scheme is depicted in FIG. 2. It is different from any other because it uses a duplex oligonucleotide array with 3'-ended single-stranded overhangs. The duplex portion of each DNA shown is constant. Only the overhangs vary, and in principle an array of 4^n probes is needed to represent all possible overhangs of length n. The advantage of such an array is that it provides enhanced sequence stringency in detecting the 5' terminal nucleotide of the target DNA because of base stacking between the preformed DNA duplex and the newly formed duplex.
>
> One variable is the length of the single-stranded overhang. The shorter the overhang, the smaller the array of probes potentially useable. [*emphasis added*]

Thus, the section of the specification recited by the Examiner teaches that "one variable" in sequencing by hybridization is the length of the single-stranded overhang. Further, the following paragraph, at page 30, lines 18-21 teaches:

> Another variable is the nucleic acid capacity of the immobilized spot of probe. This determines the detection sensitivity required and is also important where unlabeled DNA may be present that could hybridize competitively with the desired labeled DNA product. [*emphasis added*]

Thus, the instant specification does not define the recitation "variable" as "varying in length" as alleged by the Examiner. Instead, the cited section provides a number of variables in sequencing by hybridization. Further, the Examiner's argument is inapt, as pending claims 70, 72, 73 and 77-79 no longer include the recitation "variable."

Deugau *et al.* does not disclose a probe that includes a random nucleotide sequence that is not at the terminus of the single-stranded portion. The Examiner alleges that claim 33 of Deugau *et al.* discloses the array of instant claim 70. Claim 33 of Deugau *et al.* states

> 33. In a polymerase chain reaction kit comprising: heat source, oligonucleotide primers, DNA polymerase and a mixture of all four deoxynucleotide precursors, wherein the improvement comprises:
>
> a panel for obtaining indexed DNA fragments from a mixture of DNA fragments, for identifying, isolating, mapping, amplifying, or sequencing said fragments,
>
> said panel comprising a set of indexing linkers, each said indexing linker being a DNA duplex having one 3'- or 5'-protruding single strand of a length corresponding to the 3'- or 5'-protruding single strand of the cleavage site of a Type IIS restriction endonuclease or a restriction endonuclease recognizing interrupted palindromic sequences, wherein said set comprises a collection of indexing linkers whose 3'- or 5'-protruding single strands collectively encode up to all possible permutations and combinations of the nucleotides, A, C, G and T, and wherein said indexing linkers are physically separated from each other on the basis of the identity of their 3'- or 5'-protruding single strand.

Applicant respectfully submits that claim 33 does not disclose an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence within the single-stranded portion that is <u>not at the terminus</u> of the single-stranded region.

Figure 2 of Deugau *et al.* illustrates a set of probes that have variable sequences at the **terminus** of the probes. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each **end** of a fragment (col. 7, lines 48-60). Thus, because the restriction endonucleases produce terminal overhangs, the index

linkers of Deugau *et al.* do not include a random sequence that is not terminal. Hence, Deugau *et al.* does not disclose every element of the claimed subject matter of claim 70 and its dependent claims. Therefore, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 70, 72, 73 and 77-79.

REBUTTAL TO EXAMINER'S ARGUMENTS

The Examiner alleges that

> because the single-stranded portions of Deugau *et al.* have a terminal nucleotide and the number of nucleotides between the terminal nucleotide and the double-stranded portion of the probe varies, the variable single-stranded sequence would be interpreted as being not at the terminus, but instead between the terminus and the double-stranded portion.

It appears that the Examiner is arguing that the terminal nucleotide is invariable in Deugau *et al.* Applicant respectfully submits that the Examiner offers no support for this argument. Deugau *et al.* does not disclose that the terminal nucleotide does not vary or is in some manner held constant. Instead, Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each **end** of a fragment (col. 7, lines 48-60). Thus, Deugau *et al.* does not disclose producing overhangs that include random sequences that are not at the terminus of the single-chain portion.

Claims 74-76, 92-94, 123, 124 and 136

The Examiner alleges that claims 74-76, 92-94, 123, 124 and 136 include "numerous method steps for making the array of probes, *e.g.* hybridizing, ligating" and "that patentability of a product is based on the product, not the method of making the product" and contends that the claimed arrays are interpreted based on the resulting product. As a preliminary matter, applicant respectfully submits that none of claims 74-76, 92-94, 123, 124 or 136 includes "hybridizing" or "ligating" as a recitation. Claim 74 includes the recitations "the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having

a double-stranded portion and a single-stranded portion" and "the oligonucleotide is ligated to the variable sequence of the second nucleic acid."

The instant claims do not have method or process step limitations. The Examiner is reminded that

> 35 U.S.C. 101 defines four categories of inventions that Congress deemed to be the appropriate subject matter of a patent; namely, processes, machines, manufactures and compositions of matter. The latter three categories define "things" while the first category defines "actions" (i.e., inventions that consist of a series of steps or acts to be performed). See 35 U.S.C. 100(b).

See MPEP 2106(IV)(A). The instant claims do not include a series of steps or acts to be performed. What the Examiner characterizes as method steps are structural limitations imposed on the claimed array. Claim 74 requires that the first nucleic acid be hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion. Thus, the limitation precludes a probe where the first nucleic acid hybridized to the second nucleic acid forms a hybrid lacking a single-stranded portion. Similarly, claim 74 requires that the oligonucleotide be ligated to the random nucleotide sequence of the second nucleic acid. This limitation precludes the oligonucleotide from being ligated to the first nucleic acid. Further, this limitation results in a single-stranded region having a length of between about 7 to about 30 nucleotides (a random terminal nucleotide sequence of between 3-10 nucleotides in length ligated to an oligonucleotide of about 4-20 nucleotides in length). Thus, the limitations are not method steps. The limitations define certain structural attributes of the claimed array. Hence, these limitations must be accorded patentable weight and considered.

Deugau *et al.* does not disclose an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 and a longer single-stranded second nucleic acid of about 20-30 nucleotides having a random terminal nucleotide sequence of between about 3-10 nucleotides ligated to an oligonucleotide of about 4-20 nucleotides that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second

nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion.

As discussed above, Deugau *et al.* discloses that its indexing linkers are terminated by overhangs produced by cleavage with restriction endonucleases and are of a length of 3, 4, or 5 nucleotides. Deugau *et al.* does not disclose an array of probes where each probe has a double-stranded region and a single-stranded region, where the single-stranded region is greater than 5 nucleotides in length as instantly claimed (the single-stranded region includes a random terminal nucleotide sequence of between 3-10 nucleotides in length ligated to an oligonucleotide of about 4-20 nucleotides in length).

Hence, Deugau *et al.* does not disclose every element of the claimed subject matter of claim 74 and its dependent claims. Therefore, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 74-76, 92-94, 123, 124 and 136.

Claims 127-133, 135, 137 and 138

The Examiner alleges that claims 127-133, 135, 137 and 138 include "numerous method steps for making the array of probes, *e.g.* dividing the probes and/or designing the probes and/or mental steps for defining or designing the single-stranded portions of the probe" and "that patentability of a product is based on the product, not the method of making the product" and contends that the claimed arrays are interpreted based on the resulting product. As a preliminary matter, applicant respectfully submits that none of claims 127-133, 135, 137 and 138 includes "dividing the probes" as a recitation. Claim 127 includes the recitation "the array is divided into subarrays."

The instant claims do not have method step limitations. What the Examiner characterizes as method steps are structural limitations imposed on the claimed array. For example, claim 127 requires the single-stranded portion of each probe to include a predetermined sequence of fixed and non-fixed positions. Claim 127 also requires that the array be divided into subarrays, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions

of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base. For example, by having the array divided into subarrays as claimed, the number of probes required for a nucleic acid sequence of length k can be reduced from 4^k probes to $4(2^{k-1})$ probes (see page 12, lines 3-9). Thus, the limitations define certain structural attributes of the claimed array, and are not method step limitations. Hence, these limitations must be accorded patentable weight and considered.

Deugau *et al.* discloses that its comprehensive panel of indexing linkers contains all possible combinations and permutations of the nucleotides A, C, G and T. Deugau *et al.* does not disclose an array of nucleic acid probes where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions. Deugau *et al.* does not disclose an array where within the array the probes are divided into subarrays; and in each subarray, within the single-stranded portion of each probe, a selected base of the nucleic acid occupies the fixed positions and all other bases except the selected base are used in the non-fixed positions.

Hence, Deugau *et al.* does not disclose every element of the claimed subject matter of claim 127 and its dependent claims. Therefore, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 127-133, 135, 137 and 138.

REBUTTAL TO EXAMINER'S ARGUMENTS

> The Examiner alleges on page 9, lines 17-19 of the Office Action that the single-stranded portions of Deugau *et al.* inherently have one base at fixed positions and unfixed positions and the other bases would be in the remaining positions.

Applicant respectfully submits that claim 127 is directed to an array of probes that includes as a limitation that the single-stranded portion of each probe include a predetermined sequence of fixed and non-fixed positions, and the array is divided into subarrays, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and **all other**

bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base. Thus, the argument that the "single-stranded portions of Deugau *et al.* inherently have one base at fixed positions and unfixed positions" is inapt.

Further, applicant respectfully submits that the single-stranded portions of Deugau *et al.* **do not** inherently have one base at fixed positions and all other bases except the selected base in the non-fixed positions as instantly claimed. This is evidenced by the fact that Deugau *et al.* discloses that the minimum number of probes required for its comprehensive panel for a nucleic acid sequence of length k is $[N \times (N+1)] \div 2$, where $N = 4^k$ (see col. 7, lines 53-64 and col. 8, lines 37-39). The instant application discloses that by dividing the array into subarrays as instantly claimed, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base, the number of probes required for a nucleic acid sequence of length k can be reduced from 4^k probes to $4(2^{k-1})$ probes (*e.g.*, see page 12, lines 3-9).

REJECTION OF CLAIMS 73, 123, 128 AND 138 UNDER 35 U.S.C. §103(a)

Claim 73, 123, 128 and 138 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deugau *et al.* in view of Brenner *et al.* (*Proc. Natl. Acad. Sci. USA*, 1989, 86:8902-8906) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except the specific means by which the probes are immobilized, but Brenner *et al.* allegedly cures this defect. The Examiner alleges that Brenner *et al.* teaches that biotin/streptavidin provides a versatile means of capture immobilization.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital*

Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp*. 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 73 depends from claim 70, and claim 123 depends from claim 74. Claim 73 and claim 123 are directed to an embodiment where the probes are fixed to a solid support by conjugating to a coupling agent selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Claim 138 depends from claim 127 and is directed to an embodiment where the probes are fixed to a solid support by conjugating to a coupling agent. Claim 128 depends from claim 138 and is directed to an embodiment where the coupling agent is selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Teachings of the Cited References

Deugau *et al.*

See related section above.

Brenner *et al.*

Brenner *et al.* teaches a fluorescent DNA sequence fingerprinting procedure that couples band separation with sampled nucleotide sequencing (page 8902, right column, lines 11-14). The reference teaches cleaving DNA using endonuclease followed by electrophoresis and analysis by fluorescent emissions (paragraph bridging pages 8902-8903). Brenner *et al.* teaches that following specific cleavage using any restriction enzyme, biotin can be attached to each primary cleavage end by adding biotinylated nucleotides (page 8904, left column, second full paragraph).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Brenner *et al.* does not result in the instantly claimed arrays.

Claim 73

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of nucleic acid probes having a random sequence within the single-stranded portion that is not at the terminus. Brenner *et al.* does not cure this defect.

Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* does not teach or suggest a probe having a double-stranded region, a terminal single-stranded region and a random sequence within the single-stranded region that is not at the terminus.

As shown in Figure 4, after specific cleavage, all of the resulting fragments have a single-stranded region on both ends (page 8904). Brenner *et al.* does not teach or suggest including a non-terminal random sequence within the single-stranded region. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 73.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded region and a random nucleotide sequence within the single-stranded portion that is not at the terminus. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed arrays of claim 73. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 123

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of probes where each probe has a double-stranded region and a single-stranded region, where the single-stranded region has a length of between about 7 to about 30 nucleotides.

Brenner *et al.* does not cure this defect. Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA using restriction enzymes or other methods of specific cleavage, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* teaches single-stranded ambiguous overhangs of 1, 2 and 4 nucleotides in length (see Fig 1., page 8903). Brenner *et al.* does not teach or suggest a probe having

a double-stranded region, and a terminal single-stranded region of between about 7 to about 30 nucleotides in length. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 123.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed array of claim 123. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 128 and 138

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of probes where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions, nor an array where within the array the probes are divided into subarrays and in each subarray, within the single-stranded portion of each probe, a selected base of the nucleic acid occupies the fixed positions and all other bases except the selected base are used in the non-fixed positions.

Brenner *et al.* does not cure this defect. Brenner *et al.* teaches using a type of restriction enzyme that leaves a 5′ overhang where the sequence of the

5' overhang is not unique and can consist of several different nucleotide combinations (see page 8903, left column, last paragraph). Brenner *et al.* does not teach or suggest an array of probes where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions, nor an array where within the array the probes are divided into subarrays and in each subarray, within the single-stranded portion of each probe, a selected base of the nucleic acid occupies the fixed positions and all other bases except the selected base are used in the non-fixed positions. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 128 or 138.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions, and the array is divided into subarrays, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed array of claims 128 or 138. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 75 AND 132 UNDER 35 U.S.C. §103(a)

Claims 75 and 132 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deugau *et al.* in view of Ghosh *et al.* (*J. Chem Inf. Comput. Sci.* 38: 1161-70 (1998)) because Deugau *et al.* allegedly teaches every element

of the claimed subject matter except conjugation of the probe to the support through a coupling agent, but Ghosh *et al.* allegedly cures this defect.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 75 depends from claim 74 and is directed to an embodiment where the array is fixed to a solid support selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Claim 132 depends from claim 127 and is directed to an embodiment where the solid support is selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Teachings of the Cited References

Deugau *et al.*

See related section above.

Ghosh *et al.*

Ghosh *et al.* teaches the direct covalent attachment of DNA to solid supports derivatized with alkyl-amino and alkyl-carboxylic functionalities. Ghosh *et al.* teaches covalently attaching oligonucleotides having a length of 17-29 bases to a solid support (page 5353 and page 5363) Ghosh *et al.* teaches a number of chemical methods for the attachment of DNA to solid supports through stable covalent linkages, including carbodiimide-mediated end attachment or phosphodiester bonds (page 5354). Ghosh *et al.* teaches covalently attaching DNA oligonucleotides to solid supports by conversion to phosphoramidate derivatives that react with amino or carboxyl functionalities on the support surface (pages 5359-60 and 5369). Ghosh *et al.* teaches methods of preparation of 5'-aminohexyl and 5'-cystaminyl phosphoramidate derivatives of the oligonucleotides (page 5358).

Ghosh *et al.* does not teach or suggest an oligonucleotide having a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. Ghosh *et al.* does not teach or suggest a single-stranded portion of a probe that includes a predetermined sequence of fixed and non-fixed positions. Ghosh *et al.* does not teach or suggest dividing an array of nucleic acid probes into subarrays where within each subarray a selected base occupies the fixed positions and all other bases except the selected base occupy the non-fixed positions in the single-stranded portion. Ghosh *et al.* does not teach or suggest covalent attachment of ribonucleic acid or protein nucleic acid to solid supports.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Ghosh *et al.* does not result in the instantly claimed arrays.

Claim 75

Claim 75 depends from claim 74 and is directed to embodiment of an array of probes each of which contains a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. As discussed above, Deugau *et al.* does not teach or suggest an array of probes each of which includes a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

Ghosh *et al.* does not cure this defect. Ghosh *et al.* does not teach or suggest an array of nucleic probes, nor does Ghosh *et al.* teach or suggest a probe that includes a double-stranded portion, a terminal single-stranded and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. Ghosh *et al.* provides limited information on the oligonucleotides used, teaching their length (page 5353 and page 5363) and methods of derivatizing the oligonucleotides (page 5358). Hence, even if, arguendo, Ghosh *et al.*

teaches covalent coupling of oligonucleotides to a solid support, combining the teachings of Deugau *et al.* and Ghosh *et al.* does not teach or suggest every element of claim 75.

Neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed arrays of claim 75. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 132

Deugau *et al.* discloses that its comprehensive panel of indexing linkers contains all possible combinations and permutations of the nucleotides A, C, G and T. Deugau *et al.* does not teach or suggest an array of nucleic acid probes where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions. Deugau *et al.* does not teach or suggest an array where within the array the probes are divided into subarrays; and in each subset, within the single-stranded portion of each probe, a selected base of the nucleic acid occupies the fixed positions and all other bases except the selected base are used in the non-fixed positions.

Ghosh *et al.* does not cure this defect. Ghosh *et al.* does not teach or suggest an array of nucleic acid probes where the probes have a single-stranded portion at one terminus and a double-stranded portion at the opposite terminus, where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed position. Ghosh *et al.* does not teach or suggest dividing an array of probes into subarrays. Ghosh *et al.* does not teach or suggest selecting a base of the nucleic acid to occupy the fixed positions and

using all other bases except the selected base in the non-fixed positions. Hence, even if, arguendo, Ghosh *et al.* teaches covalent coupling of oligonucleotides to a solid support, combining the teachings of Deugau *et al.* and Ghosh *et al.* does not teach or suggest every element of claim 132.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed array of claim 132. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Stephanie Seidman

SUPPORTING DOCUMENT

1. *Merriam Webster's Collegiate Dictionary,* (Tenth ed., 1995, page 1359).

Merriam-Webster's Collegiate® Dictionary

TENTH EDITION

Merriam-Webster, Incorporated
Springfield, Massachusetts, U.S.A.

A GENUINE MERRIAM-WEBSTER

The name *Webster* alone is no guarantee of excellence. It is used by a number of publishers and may serve mainly to mislead an unwary buyer.

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witch-es'-broom \'wi-chəz-ˌbrüm, -ˌbrüm\ *n* (1881) : an abnormal tufted growth of small branches on a tree or shrub caused esp. by fungi or viruses

witches' Sabbath *n* (ca. 1676) : a midnight assembly of witches, devils, and sorcerers for the celebration of rites and orgies

witch-grass \'wich-ˌgras\ *n* [prob. alter. of *quitch (grass)*] (1790) 1 : QUACK GRASS 2 [*witch*]: a No. American grass (*Panicum capillare*) with slender brushy panicles that is often a weed on cultivated land

witch ha-zel \'wich-ˌhā-zəl\ *n* [*witch*, a tree with pliant branches, fr. ME *wyche*, fr. OE *wice*; prob. akin to OE *wican* to yield — more at WEAK] (ca. 1542) : 1 : any of a genus (*Hamamelis* of the family Hamamelidaceae, the witch-hazel family) of shrubs or small trees with slender-petaled yellow flowers borne in late fall or early spring; *esp* : one (*H. virginiana*) of eastern No. America that blooms in the fall 2 : an alcoholic solution of a distillate of the bark of a witch hazel (*H. virginiana*) used as a soothing and mildly astringent lotion

witch-hunt \'wich-ˌhənt\ *n* (1885) 1 : a searching out for persecution of persons accused of witchcraft 2 : the searching out and deliberate harassment of those (as political opponents) with unpopular views — **witch-hunt-er** *n* — **witch-hunt-ing** *n or adj*

witch-ing \'wi-chiŋ\ *n* (bef. 12c) : the practice of witchcraft : SORCERY

witching *adj* (14c) : of, relating to, or suitable for sorcery or supernatural occurrences ⟨the very ~ time of night —Shak.⟩

witch of Agne-si \'wi-ən-yä-zē\ *n* [Maria Gaetana *Agnesi* †1799 Ital. mathematician; *witch*, trans. of It *versiera* cubic curve (influenced by It *versiera* female demon)] (1875) : a plane cubic curve that is symmetric about the y-axis and approaches the x-axis as an asymptote that is constructed by drawing lines from the origin intersecting an upright circle tangent to the x-axis at the origin and taking the locus of points of intersection of pairs of lines parallel to the x-axis and y-axis each pair of which consists of a line parallel to the x-axis through the point where a line through the origin intersects the circle and a line parallel to the y-axis through the point where the same line through the origin intersects the line parallel to the x-axis through the point of intersection of the circle and the y-axis and that has the equation $x^2y = 4a^2(2a - y)$ — called also *witch*

witch-weed \'wich-ˌwēd\ *n* (1904) : any of a genus (*Striga*) of yellow-flowered Old World plants of the snapdragon family that are damaging root parasites of grasses (as sorghum and maize) and that include one (*S. lutea*) which is an introduced pest in parts of the southeastern U.S.

wite \'wīt\ *vt* **wit-ed; wit-ing** [ME, fr. OE *witan*, akin to OHG *wizan* to blame, OE *witan* to know] (bef. 12c) *chiefly Scot* : BLAME

wite *n* (13c) *chiefly Scot* : BLAME, RESPONSIBILITY

wi-te-na-ge-mot *or* wi-te-na-ge-mote \'wi-tᵊn-ə-gə-ˌmōt, -yə-ˌmōt\ *n* [OE *witena gemōt*, fr. *witena* (gen. pl. of *wita* sage, adviser) + *gemōt* gemot] (bef. 12c) : an Anglo-Saxon council made up of a varying number of nobles, prelates, and influential officials and convened from time to time to advise the king on administrative and judicial matters

with \'with, 'with, wəth, wəth\ *prep* [ME, against, from, with, fr. OE; akin to OE *wither* against, OHG *widar* against, back, Skt *vi* apart] (bef. 12c) 1 *a* : in opposition to : AGAINST ⟨had a fight ~ his brother⟩ *b* so as to be separated or detached from ⟨broke ~ her family⟩ 2 *a* used as a function word to indicate a participant in an action, transaction, or arrangement ⟨works ~ his father⟩ ⟨a talk ~ a friend⟩ ⟨got into an accident ~ the car⟩ *b* used as a function word to indicate the object of attention, behavior, or feeling ⟨get tough ~ him⟩ ⟨angry ~ her⟩ *c* : in respect to : so far as concerns ⟨on friendly terms ~ all nations⟩ *d* used to indicate the object of an adverbial expression of imperative force ⟨off ~ his head⟩ *e* : OVER, ON ⟨no longer has any influence ~ them⟩ *f* : in the performance, operation, or use of ⟨the trouble ~ this machine⟩ 3 *a* used as a function word to indicate the object of a statement of comparison or equality ⟨a dress identical ~ her hostess's⟩ *b* used as a function word to express agreement or sympathy ⟨must conclude, ~ you, that the painting is a forgery⟩ *c* on the side of : FOR ⟨if he's for lower taxes, I'm ~ him⟩ *d* : as well as ⟨can pitch ~ the best of them⟩ 4 *a* used as a function word to indicate combination, accompaniment, presence, or addition ⟨heat milk ~ honey⟩ ⟨went there ~ her⟩ ⟨his money, ~ his wife's, comes to a million⟩ *b* : inclusive of ⟨costs $5 ~ the tax⟩ 5 *a* : in the judgment or estimation of ⟨stood well ~ her classmates⟩ *b* : in or according to the experience or practice of ⟨~ many of us, our ideas seem to fall by the wayside —W. J. Reilly⟩ 6 *a* used as a function word to indicate the means, cause, agent, or instrumentality ⟨hit him ~ a rock⟩ ⟨pale ~ anger⟩ ⟨threatened ~ tuberculosis⟩ ⟨he amused the crowd ~ his antics⟩ *b archaic* : by the direct act of 7 *a* used as a function word to indicate manner of action ⟨ran ~ effort⟩ ⟨acknowledge your contribution ~ thanks⟩ *b* used as a function word to indicate an attendant fact or circumstance ⟨stood there ~ his hat on⟩ *c* used as a function word to indicate a result attendant on a specified action ⟨got off ~ a light sentence⟩ 8 *a* (1) : in possession of : HAVING ⟨came ~ good news⟩ (2) : in the possession or care of ⟨left the money ~ her mother⟩ *b* : characterized or distinguished by ⟨a person ~ a sharp nose⟩ 9 *a* used as a function word to indicate a close association in time ⟨~ the outbreak of war they went home⟩ ⟨mellows ~ time⟩ *b* in proportion to ⟨the pressure varies ~ the depth⟩ 10 *a* : in spite of : NOTWITHSTANDING ⟨a really tip-top man, ~ all his wrongheadedness —H. J. Laski⟩ *b* except for ⟨finds that, ~ one group of omissions and one important addition, they reflect that curriculum —Gilbert Highet⟩ 11 : in the direction of ⟨~ the wind⟩ ⟨~ the grain⟩

with-al \wi-'thȯl, -'thōl\ *adv* [ME, fr. *with* + *all, al* all] (13c) 1 : together with this : BESIDES ⟨a supporter of all constructive work and ~ an excellent businessman —A. W. Long⟩ 2 *archaic* : THEREWITH 3 : on the other hand : NEVERTHELESS

withal *prep* (14c) *archaic* : WITH — used postpositively with a relative or interrogative pronoun as object

with-draw \with-'drȯ, with-\ *vb* **-drew** \-'drü\; **-drawn** \-'drȯn\; **-draw-ing** \-'drȯ(-ə)riŋ\ [ME, fr. *with* from + *drawen* to draw] *vt* (13c) 1 *a* : to take back or away : REMOVE ⟨pressure upon educational administrators to ~ academic credit —J. W. Scott⟩ *b* : to remove from use or cultivation *c* : to remove (money) from a place of deposit *d* : to turn away (as the eyes) from an object of attention ⟨withdrew her gaze⟩ *e* : to draw (as a curtain) back or aside 2 *a* : to remove from consideration or set outside a group ⟨*withdrew* his name from the list of nominees⟩ ⟨*withdrew* their child from the school⟩ *b* (1) : TAKE BACK, RETRACT (2) : to recall or remove (a motion) under parliamentary procedure — *vi* 1 *a* : to move back or away : RETIRE *b* : to draw back from a battlefield : RETREAT 2 *a* : to remove oneself from participation *b* : to become socially or emotionally detached ⟨had *withdrawn* farther and farther into herself —Ethel Wilson⟩ 3 : to recall a motion under parliamentary procedure — **with-draw-able** \-'drȯ-ə-bəl\ *adj*

with-draw-al \-'drȯ(-ə)l\ *n* (1749) 1 *a* : the act of taking back or away something that has been granted or possessed *b* : removal from a place of deposit or investment *c* (1) : the discontinuance of administration or use of a drug (2) : a period following the discontinuance of an addicting drug that is marked by often painful physical and psychological symptoms ⟨a heroin addict going through ~⟩ 2 *a* : retreat or retirement esp. into a more secluded or less exposed place or position *b* : an operation by which a military force disengages from the enemy *c* (1) : social or emotional detachment (2) : a pathological retreat from objective reality (as in some schizophrenic states) 3 : RETRACTION, REVOCATION ⟨threatened us with ~ of consent⟩ 4 *a* the act of drawing someone or something back from or out of a place or position *b* : COITUS INTERRUPTUS

withdrawing room *n* (1591) : a room to retire to (as from a dining room); *esp* : DRAWING ROOM

with-drawn \with-'drȯn, with-\ *adj* (1615) 1 : removed from immediate contact or easy approach : ISOLATED 2 : socially detached and unresponsive : exhibiting withdrawal : INTROVERTED — **with-drawn-ness** \-'drȯn-nəs\ *n*

withe \'with, 'with\ *n* [ME, fr. OE *withthe*; akin to OE *withig* withy] (bef. 12c) : a slender flexible branch or twig; *esp* : one used as a band or line

¹wither \'wi-thər\ *vb* **with-ered; with-er-ing** \'with-riŋ, 'wi-thə-\ [ME *widren*; prob. akin to ME *weder* weather] *vi* (14c) 1 : to become dry and sapless; *esp* : to shrivel from or as if from loss of bodily moisture 2 : to lose vitality, force, or freshness ⟨~ *vt* 1 : to cause to wither 2 : to make speechless or incapable of action : STUN ⟨~*ed* him with a look —Dorothy Sayers⟩

²wither *n* (1607) *chiefly Brit* : WITHERS

withering *adj* (1579) : acting or serving to cut down or destroy : DEVASTATING ⟨a ~ fire from the enemy⟩ — **with-er-ing-ly** \'with-riŋ-lē, 'wi-thə-\ *adv*

with-er-ite \'wi-thə-ˌrīt\ *n* [G *Witherit*, irreg. fr. William *Withering* †1799 Eng. physician] (1794) : a mineral consisting of a carbonate of barium in the form of white or gray twin crystals or columnar or granular masses

withe rod *n* (1846) : a No. American viburnum (*Viburnum cassinoides*) with tough slender shoots

with-ers \'wi-thərz\ *n pl* [prob. fr. obs. E *wither* against, fr. ME, fr. OE fr. *wither* against; fr. the withers being the parts which resist the pull in drawing a load — more at WITH] (1580) 1 : the ridge between the shoulder bones of a horse — see HORSE illustration 2 : a part corresponding to the withers in a quadruped other than a horse

with-er-shins \'wi-thər-shənz\ *var of* WIDDERSHINS

with-hold \with-'hōld, with-\ *vb* **-held** \-'held\; **-hold-ing** [ME, fr. *with* from + *holden* to hold — more at WITH] *vt* (13c) 1 : to hold back from action : CHECK 2 *archaic* : to keep in custody 3 : to refrain from granting, giving, or allowing ⟨~ permission⟩ 4 : to deduct (withholding tax) from income ⟨~ *vi* : FORBEAR, REFRAIN *syn* see KEEP — **with-hold-er** *n*

withholding tax *n* (1940) : a deduction (as from wages, fees, or dividends) levied at a source of income as advance payment on income tax

¹within \wi-'thin, -'thin\ *adv* [ME *withinne*, fr. OE *withinnan*, fr. *with* + *innan* inwardly, within, fr. *in*] (bef. 12c) 1 : in or into the interior : INSIDE 2 : in one's inner thought, disposition, or character : INWARDLY ⟨search ~ for a creative impulse —Kingman Brewster, Jr.⟩

²within *prep* (12c) 1 — used as a function word to indicate enclosure or containment 2 — used as a function word to indicate situation or circumstance in the limits or compass of: as *a* : before the end of ⟨gone ~ a week⟩ *b* (1) : not beyond the quantity, degree, or limitations of ⟨live ~ your income⟩ (2) : in or into the scope or sphere of ⟨~ the jurisdiction of the state⟩ (3) : in or into the range of ⟨~ reach⟩ ⟨~ sight⟩ (4) — used as a function word to indicate a specified difference or margin ⟨came ~ two points of a perfect mark⟩ ⟨~ a mile of the town⟩ 3 : to the inside of : INTO 4

³within *n* (15c) : an inner place or area ⟨revolt from ~⟩

⁴within *adj* (1748) : being inside : ENCLOSED ⟨the ~ indictment⟩

with-in-doors \wi-thin-'dōrz, -thin-\ *adv* (1581) : INDOORS

with-it \'wi-thət, -thət\ *adj* (1959) : socially or culturally up-to-date ⟨the intelligent, dissaffected, ~ young —Eliot Fremont-Smith⟩

¹with-out \wi-'thau̇t, -'thau̇t\ *prep* [ME *withoute*, fr. OE *withūtan*, fr. *with* + *ūtan* outside, fr. *ūt* out — more at OUT] (bef. 12c) 1 : OUTSIDE 2 — used as a function word to indicate the absence or lack of something or someone ⟨fight ~ fear⟩ ⟨left ~ him⟩ ⟨looks ~ seeing⟩

²without *adv* (bef. 12c) 1 : on the outside : EXTERNALLY 2 : with something lacking or absent ⟨has learned to do ~⟩

³without *conj* (14c) *chiefly dial* : UNLESS ⟨you don't know about me ~ you have read a book —Mark Twain⟩

⁴without *n* (15c) : an outer place or area ⟨came from ~⟩

with-out-doors \wi-ˌthau̇t-'dōrz, -ˌthau̇t-\ *adv* (1617) : OUTDOORS

with-stand \with-'stand, with-\ *vt* **-stood** \-'stu̇d\ **-stand-ing** [ME, fr. OE *withstandan*, fr. *with* against + *standan* to stand] (bef. 12c) 1 *a* : to stand up against : oppose with firm determination; *esp* : to resist successfully *b* : to be proof against : resist the effect of ⟨~ the impact of a landing —*Current Biog.*⟩ 2 *archaic* : to stop or obstruct the course of *syn* see OPPOSE

withy \'wi-thē\ *n, pl* **with-ies** [ME, fr. OE *withig*; akin to OHG *wida* willow, L *vitis* vine, *viere* to plait — more at WIRE] (bef. 12c) 1 : WILLOW, *esp* : OSIER 2 : a flexible slender twig or branch (as of osier) : WITHE

\ə\ abut \ˈ\ kitten, F table \ər\ further \a\ ash \ā\ ace \ä\ mop, mar \au\ out \ch\ chin \e\ bet \ē\ easy \g\ go \i\ hit \ī\ ice \j\ job \ŋ\ sing \ō\ go \ȯ\ law \ȯi\ boy \th\ thin \t͟h\ the \ü\ loot \u̇\ foot \y\ yet \zh\ vision \à, ḵ, ṗ, œ, œ̄, ue, ue̅, ˆ\ see Guide to Pronunciation